Vaccine 29 (2011) 3633–3639

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A prospective, randomized, open-label trial comparing the safety and efficacy of trivalent live attenuated and inactivated influenza vaccines in adults 60 years of age and older

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ARTICLE INFO

Article history:
Received 3 December 2010
Received in revised form 4 March 2011
Accepted 10 March 2011
Available online 5 April 2011

Keywords:
Adults
Clinical trial
Influenza
Live attenuated influenza vaccine
Trivalent inactivated influenza vaccine

ABSTRACT

Background: Although influenza is a major public health concern among adults ≥60 years of age, few large, prospective studies of influenza vaccines have been conducted in this population. The goal of the present study was to directly compare the safety and efficacy of LAIV and TIV in adults ≥60 years of age.
Materials and methods: A prospective, randomized, open-label, multicenter trial was conducted in South Africa. In March–April 2002, 3009 community-dwelling ambulatory adults 60–95 years of age were randomized 1:1 to receive a single dose of LAIV or TIV. Surveillance for influenza illness was conducted through November. Serum antibody titers were evaluated in all participants, and interferon-γ enzyme-linked immunosorbent spot assay responses were evaluated in a cohort of subjects. Solicited reactogenicity and adverse events were monitored for days 0–10 postvaccination; serious adverse events were monitored for the entire study.
Results: Influenza illness caused by vaccine-matched strains was detected in 0.8% (12/1494) and 0.5% (8/1488) of LAIV and TIV recipients, respectively; the relative efficacy of LAIV vs TIV was −49% (95% CI: −259, 35). As expected, greater serum antibody responses were seen with TIV, and greater cellular responses were seen with LAIV (although not for influenza B). Among subjects with culture-confirmed influenza illness, post hoc analyses revealed trends toward less feverishness (LAIV, 14%; TIV, 46%; $P = 0.05$) and less fever (LAIV, 9%; TIV, 31%; $P = 0.16$) among LAIV recipients. In each treatment group, 38–39% and 24–25% of subjects had baseline hemagglutination inhibition titers of ≤4 for A/H1 and A/H3, but 7 of 8 TIV cases and 7 of 12 LAIV cases of matched-strain influenza occurred among these subjects. Runny nose/nasal congestion (+13%), cough (+5%), sore throat (+5%), lethargy (+3%), and decreased appetite (+2%) were reported by more LAIV vs TIV recipients. Injection site reactions were reported by 27% of TIV recipients. SAEs were reported by a similar proportion of LAIV and TIV recipients (9% vs 8%).
Conclusions: Given the low incidence of influenza in both groups, no conclusions were possible regarding the relative efficacy of LAIV and TIV. There was a trend toward less feverishness/fever among LAIV recipients who developed influenza compared with TIV recipients with influenza, consistent with results from studies comparing the vaccines in children. A disproportionate number of influenza illnesses occurred among baseline seronegative subjects, particularly for those receiving TIV, which suggests that this subgroup has the greatest need for improved influenza vaccination. The safety profiles of LAIV and TIV were consistent with results from previous studies in older adults and no significant safety concerns were identified.
clinicaltrials.gov identifier, NCT00192413.

Abbreviations: AE, adverse event; ELISPOT, enzyme-linked immunosorbent spot; GMFR, geometric mean fold rise; GMT, geometric mean titer; HA, hemagglutinin; HAI, hemagglutination inhibition; IFN-γ, interferon-γ; ILI, influenza-like illness; LAIV, live attenuated influenza vaccine; NA, neuraminidase; PBMC, peripheral blood mononuclear cells; SAE, serious adverse event; TIV, trivalent inactivated influenza vaccine.

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doi:10.1016/j.vaccine.2011.03.029

1. Introduction

Influenza illness is a major public health concern among older adults. Significant morbidity and mortality are attributable to influenza infection in adults ≥60 years of age with and without underlying risk factors [1]. Currently, nonadjuvanted standard-dose, nonadjuvanted high-dose, and adjuvanted inactivated vaccines are approved for use in adults ≥60 years of age. Live attenuated influenza vaccine (LAIV, MedImmune, Gaithersburg, MD, USA) is a cold-adapted, temperature-sensitive, trivalent influenza vaccine licensed in several countries for prevention of influenza in eligible children and adults 2–49 years of age; licensure in Canada is for eligible individuals 2–59 years of age,and in the European Union for eligible children 2-17 years of age [2].

Despite the importance of influenza prevention in older adults, few prospective studies of influenza vaccines have been conducted in this population. In 1991–1992, a randomized, placebo-controlled study of inactivated influenza vaccine was conducted in 1838 adults >60 years of age and demonstrated approximate 50% efficacy against serologically confirmed influenza infection and a 27–47% reduction in influenza like illness (ILI) of various definitions [3]; no safety data were reported. In 2001, a randomized, placebo-controlled study of LAIV conducted in 3242 adults >60 years of age demonstrated that LAIV was 42% efficacious against culture-confirmed influenza illness [4]. Compared with placebo, LAIV recipients experienced increased rates of runny nose/nasal congestion (+19%), cough (+6%), sore throat (+5%), headache (+5%), muscle ache (+4%), tiredness (+3%), decreased appetite (+3%), and use of fever medication (+3%) during the first 11 days postvaccination. Post hoc analyses of these two studies found different effects of age on vaccine efficacy. In adults ≥70 years of age, the efficacy of inactivated vaccine trended lower, whereas the efficacy of LAIV trended higher.

The objective of the present study was to directly compare the safety and efficacy of LAIV and trivalent inactivated influenza vaccine (TIV) in adults ≥60 years of age. Because of the critical importance of understanding the efficacy of influenza vaccines in older adults, additional analyses were conducted to describe the immune response to the vaccines and their relationships with the incidence of influenza illness.

2. Methods

2.1. Study design

A prospective, randomized, open-label, multicenter trial was conducted at 30 sites in the Republic of South Africa during the 2002 influenza season to evaluate the safety and efficacy of LAIV and TIV in adults ≥60 years of age (clinicaltrials.gov identifier, NCT00192413). Patients were randomized using treatment allocation cards at a 1:1 ratio to receive a single, open-label dose of LAIV or TIV. The original protocol and all amendments were approved by the independent ethics committees for each study site and the South African regulatory authority before initiating any study procedures. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice, and complied with all relevant national and local laws. Study results were posted publicly online in April 2008.

2.2. Participants

All study participants were community-dwelling ambulatory adults ≥60 years of age. Exclusion criteria included residence in a nursing home or long-term care facility and receipt of skilled or semiskilled nursing care, renal insufficiency requiring supportive therapy, cognitive impairment, immune dysfunction, immunosuppression or residing with an immunocompromised individual, receipt of blood products or immunoglobulin within 6 months before the study, hypersensitivity to eggs or any vaccine component, receipt of any live virus vaccine or any influenza antiviral treatment within 1 month before enrollment, or receipt of influenza vaccine within 6 months before enrollment.

2.3. Vaccines

Vaccine strains for LAIV were supplied by MedImmune (Mountain View, CA, USA). LAIV was manufactured by Wyeth (Marietta, PA, USA) and contained 3 cold-adapted, attenuated, reassortant strains representative of the hemagglutinin (HA) and neuraminidase (NA) antigens of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) (A/Moscow-like), and B/Victoria/504/2000 (B/Sichuan-like) influenza strains. Each 0.2- mL dose contained approximately 10^7 fluorescent focus units of each component virus and was administered intranasally with a spray applicator (approximately 0.1 mL into each nostril). TIV (Aventis Pasteur MSD, Lyon, France) was administered as a 0.5 mL intramuscular injection and contained 15 μg of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) (A/Moscow-like) and B/Johannesburg/5/99 (B/Sichuan-like) virus.

2.4. Surveillance for influenza-like illness

Participants were monitored by weekly telephone contact beginning 11 days postvaccination and continuing for the duration of the study. Nasal and/or throat swabs were taken at home or clinic visits within 4 days if participants reported feeling feverish, or had an oral temperature ≥37.2 F, sore throat, new or increased cough, malaise, or myalgia. Samples were cultured locally to detect virus and confirmed at the National Institute for Communicable Diseases (Sandringham, Republic of South Africa); positive isolates were serotyped using polymerase chain reaction by Wyeth (Pearl River, NY, USA).

2.5. Immunogenicity

Serum samples were collected from all participants before vaccination and 35 ± 7 days after vaccination and were tested by hemagglutination inhibition (HAI) assay for antibodies to influenza A/H3N2, A/H1N1, and B strains. Seroconversion was defined as a ≥4-fold rise in serum HAI antibody titer postvaccination [5]. A baseline HAI titer ≤1:4 was considered seronegative. Peripheral blood mononuclear cells (PBMC) for interferon (IFN)-γ enzyme-linked immunosorbent spot (ELISPOT) analysis were collected from selected subjects prevaccination (day 0) and 7–10 days postvaccination [6]. The immunogenicity population included all subjects who received a dose of LAIV or placebo and had prevaccination and postvaccination serum HAI assay results for all three influenza virus strains.

2.6. Safety

Solicited reactogenicity events, adverse events (AEs), localized reactions (TIV recipients), unscheduled physician visits, and medications were recorded by subjects for 11 days postvaccination. Serious AEs (SAEs), including hospitalizations, were monitored from enrollment through study completion. The safety population included all subjects who received a dose of LAIV or TIV.

2.7. Statistical methods and analyses

For sample size calculations, the rate of culture-confirmed influenza was assumed to be equal for LAIV and TIV recipients. A

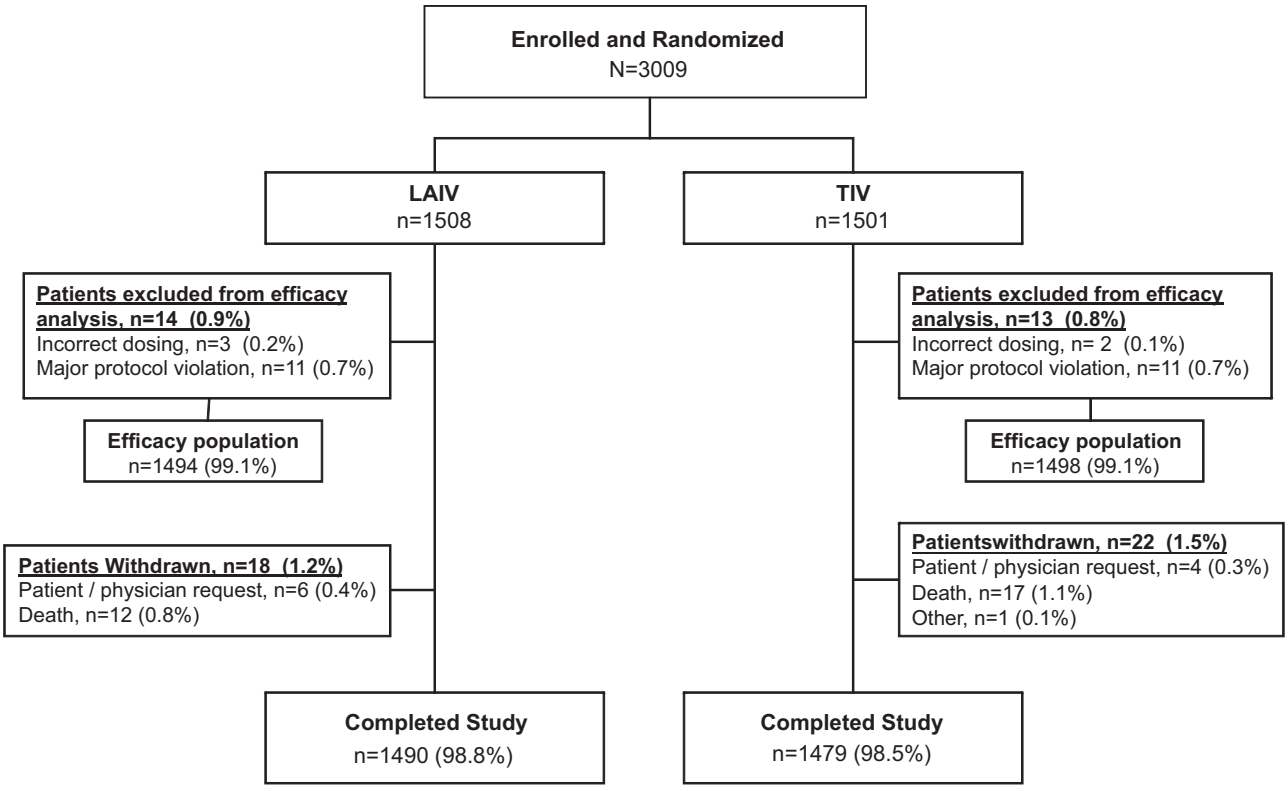

Fig. 1. Subject disposition. LAIV, live attenuated influenza vaccine and TIV, trivalent inactivated influenza vaccine.

sample size of 2440 subjects (randomized 1:1), with a drop-out rate of 18% and an influenza attack rate of 8%, was expected to provide a 90% power for the noninferiority contrast between LAIV and TIV. LAIV efficacy relative to TIV was estimated by $VE = 1 - (L/N_L)/(T/N_T)$, where N_L = number of LAIV recipients, L = number of influenza cases among LAIV recipients, N_T = number of TIV recipients, and T = number of influenza cases among TIV recipients. The proportions of subjects who seroconverted in the two treatment groups were compared using a 2-sided Fisher's exact test. Serum geometric mean antibody titers prevaccination and postvaccination and geometric mean fold rises (GMFRs) in HAI antibody from prevaccination to postvaccination were calculated. Post hoc analyses of serum HAI titers and ELISPOT counts in subjects with and without culture-confirmed influenza were conducted to explore relationships between baseline anti-influenza immunity, vaccine-induced immunity and incidence of disease. AEs and reactogenicity events occurring during the first 11 days postvaccination were compared between groups using a 2-sided Fisher's exact test.

3. Results

3.1. Study participants

This study enrolled 3009 adults who were randomized 1:1 to receive LAIV (n = 1508) or TIV (n = 1501) between March 26, 2002 and April 20, 2002 (Fig. 1). A total 2982 participants were included in the per protocol analysis (LAIV, n = 1494; TIV, n = 1488). Participants were primarily female (62.1%) and white (70.7%) with a mean ± SD age of 69.2 ± 6.8 years (range, 60–95 years). Demographic characteristics are summarized in Table 1. As expected, 90% of subjects reported underlying medical conditions, including cardiovascular disease (64%), endocrine/metabolic disease (36%), and respiratory conditions (18%).

Table 1
Demographic characteristics of the efficacy and safety population.

Characteristic	Treatment group		
	LAIV (n = 1494)	TIV (n = 1488)	Total (N = 2982)
Sex, n (%)			
Women	907 (60.7)	946 (63.6)	1853 (62.1)
Men	587 (39.3)	542 (36.4)	1129 (37.9)
Ethnic origin, n (%)[a]			
White	1056 (70.7)	1051 (70.6)	2107 (70.7)
African descent	424 (28.3)	417 (28.0)	841 (28.2)
Other	14 (0.9)	20 (1.3)	34 (1.1)
Age at vaccination, years			
Mean (SD)	69.2 (6.8)	69.3 (6.8)	69.2 (6.8)
Median	68.1	67.9	68.0
Range, years,n (%)	60.0–94.5	60.0–95.3	60.0–95.3
60 to <65	498 (33)	488 (33)	986 (33)
65 to <70	389 (26)	397 (27)	786 (26)
70 to <75	310 (21)	304 (20)	614 (21)
75 to <80	176 (12)	171 (11)	347 (12)
80 to <85	90 (6)	90 (6)	180 (6)
>85	31 (2)	38 (3)	69 (2)

LAIV, live attenuated influenza vaccine; IV, trivalent inactivated influenza vaccine.
[a] Ethnic origin was determined by self-report.

3.2. Efficacy against culture-confirmed influenza

Study participants provided 2458 (LAIV, n = 1231; TIV, n = 1227) nasal and throat swabs. Conclusive culture results were obtained for 98.5% (1212/1231) of LAIV and 97.0% (1190/1227) of TIV samples. In total, 35 cases of wild-type culture positive-influenza were detected during the study period. Strains were identified as A/H1N1/NewCaledonia/20/99-like, A/H3N2/Panama/2007/99-like and B/HongKong/330/01-like. The incidence of influenza caused by subtypes antigenically matched to vaccine strains was 0.8% (12/1508) and 0.5% (8/1501) among all LAIV and TIV recipients,

Table 2
Serum hemagglutination inhibition (HAI) conversion rates.

		HAI seroconversion[a]				
Virus subtype	Treatment group	N[b]	n[b]	(%)	GMFR (95% CI)[c]	P[d]
A/H1N1	LAIV	1474	123	(8.3)	1.3 (1.2, 1.3)	<0.001
	TIV	1469	955	(65.0)	7.9 (7.3, 8.6)	
A/H3N2	LAIV	1474	296	(20.1)	1.7 (1.6, 1.8)	<0.001
	TIV	1468	811	(55.2)	5.2 (4.8, 5.6)	
B	LAIV	1474	50	(3.4)	1.1 (1.1, 1.1)	<0.001
	TIV	1469	723	(49.2)	3.9 (3.7, 4.2)	

GMFR, geometric mean fold rise; HAI, hemagglutination inhibition; LAIV, live attenuated influenza vaccine and TIV, trivalent inactivated influenza vaccine.
[a] Seroconversion is defined as a ≥4-fold increase in HAI antibody titer relative to baseline after 1 dose.
[b] N, number of subjects with both pre- and post-vaccination antibody titers and n, number of seroconverters.
[c] Confidence limits are back transforms of a confidence interval based on Student's t-distribution for the mean logarithm of the titers.
[d] LAIV vs TIV; derived by a 2-sided, 2-sample Student's t-test on the logarithms.

respectively. The incidence of influenza by age group was similar; within each treatment group, 50% of cases occurred among individuals 60–69 and ≥70 years of age. There were no cases of influenza caused by viruses antigenically similar to the B subtype of the vaccine; however, antigenically dissimilar, opposite-lineage influenza B strains were detected in 0.6% of LAIV and 0.3% of TIV recipients. As a result, for all strains regardless of antigenic similarity, influenza incidence was 1.5% (22/1508) and 0.9% (13/1501) among LAIV and TIV recipients, respectively. Among subjects with culture-confirmed influenza illness, post hoc analyses revealed trends toward less feverishness (LAIV, 14%; TIV, 46%; $P = 0.05$) and less fever (LAIV, 9%; TIV, 31%; $P = 0.16$) among LAIV recipients.

3.3. Immunogenicity

A total of 2943 subjects (LAIV, $n = 1474$; TIV, $n = 1469$) participated in the immunogenicity analysis. The number of seronegative subjects was equivalent between groups; 38% of subjects were seronegative to A/H1N1, 24% to A/H3N2, and 40% to B. Among all subjects regardless of baseline antibody status, seroconversion rates were higher in TIV recipients compared with LAIV recipients for all strains (Table 2) and were highest in subjects seronegative at baseline. Postvaccination increases in geometric mean titer (GMT) and GMFR followed a similar trend with a statistically significant increase in TIV recipients compared with LAIV recipients.

At baseline, the number of PBMC secreting IFN-γ in response to A/H1, A/H3 and B viral antigens were similar in LAIV and TIV recipients, and ranged from 16 to 30 IFN-γ-secreting PBMC per 10^6 cells for all participants and all seronegative participants. By 7–10 days postvaccination, the number of IFN-γ-secreting cells significantly increased ($P \leq 0.016$) in all LAIV and TIV treatment groups with geometric mean of 32.5–45.6 for A/H1, 47.8–59.0 for A/H3, and 32.7–63.6 for B serotypes. Compared with TIV, LAIV recipients had larger increases in IFN-γ-secreting PBMC to A/H1 ($P < 0.041$) and A/H3 ($P < 0.035$); however, TIV recipients had greater responses to influenza B ($P < 0.001$; Table 3).

Analyses by age group (60–69 years vs ≥70 years), demonstrated similar HAI seroconversion rates, HAI GMFRs, and IFN-γ-secreting PBMC GMFRs for LAIV recipients in each age group. For TIV recipients, HAI responses were lower in individuals ≥70 years of age for each strain (A/H1N1, A/H3N2, and B), with 10% fewer individuals demonstrating seroconversion and 22–37% reductions in GMFRs relative to TIV recipients 60–69 years of age. IFN-γ-secreting PBMC GMFRs for TIV recipients were similar in each age group.

Post hoc analyses were conducted to analyze baseline and postvaccination HAI and PBMC values among subjects with and without vaccine-matched influenza illness (A/H1N1 or A/H3N2); each treatment group was analyzed separately given the observed differential immune responses to the two vaccines. Although the limited number of subjects with culture-confirmed influenza illness complicated the analysis, it was noted that, for both A/H1N1 and A/H3N2, the HAI GMT was lower among subjects with influenza illness compared with those without influenza illness (Table 4). However, the HAI GMFR and seroconversion rates were similar among those with and without influenza. Further review demonstrated that although only 38–39% and 24–25% of subjects in each treatment group had baseline HAI titers of ≤4 for A/H1 and A/H3, 7 of the 8 TIV cases and 7 of 12 LAIV cases of matched-strain influenza occurred among these subjects. Additionally, 6 of the 8 TIV recipients who developed influenza achieved postvaccination HAI titers ≥32. Analysis of PBMC values was further complicated by the fact that only a subset of the study population had PBMC values available; a review of the available data did not reveal a discernible association between the incidence of influenza illness and baseline or postvaccination PBMC values.

Table 3
Fold rises and treatment comparisons for ELISPOT assays.

Virus subtype	Treatment group	N[a]	GMFR (95% CI)[b]	P[c]
A/H1N1	LAIV	935	2.4 (2.2, 2.6)	<0.001
	TIV	918	1.6 (1.5, 1.8)	
A/H3N2	LAIV	934	2.4 (2.2, 2.6)	0.035
	TIV	917	2.1 (1.9, 2.3)	
B	LAIV	935	1.1 (1.0, 1.2)	<0.001
	TIV	918	2.0 (1.9, 2.2)	

ELISPOT, enzyme-linked immunosorbent spot; GMFR, geometric mean fold rise; LAIV, live attenuated influenza vaccine and TIV, trivalent inactivated influenza vaccine.
[a] For GMFR calculations, N is derived from subjects with both pre- and post-vaccination blood samples; response is the number that secrete interferon-γ per million peripheral blood mononuclear cells.
[b] Confidence limits are back-transformed confidence intervals based on Student's t-distribution for the mean logarithm.
[c] LAIV vs TIV; derived by a 2-sided, 2-sample Student's t-test on the logarithms.

3.4. Safety

Of the solicited reactogenicity events monitored within 11 days after vaccination, cough, sore throat, decreased activity (lethargy), decreased appetite, and runny nose/nasal congestion were reported by more subjects receiving LAIV than those receiving TIV (Table 5). Fever occurred with similar frequency in both treatment groups. As expected, local reactions were observed in TIV recipients, including pain (13.2%), redness (18.4%), and swelling (15.1%) at the injection site. Unsolicited AEs were reported in 23.4% and 22.6% of LAIV and TIV recipients, respectively. The most frequent AE was rhinitis, which was reported in 3.7% and 1.5% of LAIV and TIV recipients, respectively ($P < 0.001$). There were no other

Table 4
Baseline and postvaccination immunity in subjects with and without influenza illness.

		HAI						CMI (PBMC)					
		Prevaccination		Postvaccination		Response		Prevaccination		Postvaccination		Response
		N	GMT	Interquartile range, 25–75th	GMT	Interquartile range, 25–75th	GMFR	Seroconversion, *n* (%)	*N*	GMT	Interquartile range, 25–75th	GMT	Interquartile range, 25–75th	GMFR
TIV	A/H1N1	4	4.8	2–18	38.1	24–64	8	3 (75.0)	3	37	24–49	39.4	10–120	1.1
	No A/H1N1	1465	11.9	2–32	94.8	32–256	7.9	952 (65.0)	915	20.1	10–54	32.5	17–77	1.6
	A/H3N2	4	2.4	2–3	38.1	20–96	16	3 (75.0)	2	11	5–24	113	50–257	10.3
	No A/H3N2	1464	19.5	8–64	101	32–256	5.2	808 (55.2)	916	23.3	11–58	47.7	22–118	2.1
LAIV	A/H1N1	9	5	2–8	8	4–8	1.6	1 (11.1)	0					
	No A/H1N1	1465	10.7	2–32	13.5	4–32	1.3	122 (8.3)	935	19.1	10–52	45.6	23–113	2.4
	A/H3N2	3	10.1	2–64	10.1	2–64	1.0	0 (0.0)	3	82.8	47–157	284	78–670	1.7
	No A/H3N2	1471	18.4	8–64	31.5	16–64	1.7	296 (20.1)	932	21.3	10–57	50.7	27–127	2.4

CMI, cell-mediated immunity; GMFR, geometric mean fold rise; GMT, geometric mean titers; HAI, hemagglutination inhibition; LAIV, live attenuated influenza vaccine; PBMC, peripheral blood mononuclear cells and TIV, trivalent inactivated influenza vaccine.

significant differences in AEs across treatment groups. No participant discontinued the study because of an AE.

Serious AEs were reported by a similar proportion of LAIV and TIV recipients (9% vs 8%). One SAE of bronchopneumonia was reported in a LAIV recipient 2 days after vaccination and was considered possibly related to treatment. The patient was treated and fully recovered within 8 days; no hospitalization was required. In total, 29 deaths were reported during the study. Causes of death were not unusual for this study population, were similar in both groups, and were not considered to be related to study vaccines.

4. Discussion

Although there were numerically more cases of influenza in the LAIV treatment groups, no conclusions were possible regarding the relative efficacy of LAIV and TIV given the low incidence of influenza in both groups. The failure to obtain culture-positive virus was not due to technical difficulties or a failure to obtain specimens, but rather a lower than usual influenza attack rate in the region in 2002 [7]. In the previous year, a placebo-controlled study of LAIV was conducted in South Africa involving many of the same investigative sites, and significant influenza activity was detected in both LAIV and placebo recipients as demonstrated by a 7.5% incidence of vaccine-matched influenza illness among placebo recipients [4]. Low attack rates can be a problem in culture-confirmed efficacy studies of influenza vaccines, particularly in adult populations, which, compared with children, shed influenza virus for a shorter duration of time [8]. Several recent studies in adults have reported similar difficulties [9,10].

Despite the inconclusive results regarding the incidence of influenza, there were trends toward less feverishness and fever among LAIV recipients who developed influenza compared with TIV recipients with influenza ($P = 0.05$, 0.16 respectively). Similar findings of less febrile influenza in LAIV recipients have been observed in studies comparing LAIV and TIV in children [11,12]. Additionally, in an adult wild-type influenza challenge study of LAIV and TIV, LAIV recipients tended to have less severe influenza illness as measured by a lower symptom score and fewer days of respiratory symptoms [13]. This apparent differential in the severity of breakthrough influenza illness may be due to enhanced mucosal or cellular immunity in LAIV vs TIV recipients.

In the current study, the safety profiles of LAIV and TIV were consistent with results from previous studies in adults [4,14–16] and no significant safety concerns were identified. This study adds to the available data regarding the safety profile of LAIV in older adults and individuals with underlying medical conditions.

With regard to immunogenicity, greater serum antibody responses were seen with TIV, as expected. While serum antibody responses are believed to correlate with vaccine-induced protection with TIV, previous studies have demonstrated that serum antibody responses following LAIV vaccination are low, even in a study that demonstrated high vaccine efficacy against influenza illness [13]. Greater T-cell responses were seen with LAIV for influenza A but not for influenza B. As a live vaccine, it is not surprising that LAIV induced greater cellular immune responses against influenza A. In contrast to influenza A, the cellular immune response to influenza B among LAIV recipients was low. Two exploratory studies of immune responses to LAIV in adults 60 years of age and older were conducted before the current study with 19 and 24 subjects receiving LAIV, respectively; both studies utilized vaccine with the same B strain, B/Yamanashi/166/98. In one study ($N = 19$), little to no cellular immune response to influenza B was seen on days 6 and 13 postvaccination, with fold

Table 5
Summary of reactogenicity events occurring within 11 days postvaccination.

Reactogenicity event	LAIV		TIV		P^b
	N^a	n (%)	N	n (%)	
Any event	1435	900 (62.7)	1434	792 (55.2)	<0.001
Fever[c] ≥38.6 °C	1390	16 (1.2)	1406	20 (1.4)	0.616
Fever[c] ≥40.0 °C	1388	0	1399	0	1.000
Cough	1452	254 (17.5)	1456	179 (12.3)	0.000
Sore throat	1452	222 (15.3)	1451	148 (10.2)	0.000
Runny nose/nasal congestion	1457	534 (36.7)	1455	352 (24.0)	0.000
Headache	1456	418 (28.7)	1463	375 (25.6)	0.067
Chills	1437	74 (5.1)	1449	63 (4.3)	0.336
Muscle aches	1455	222 (15.3)	1459	220 (15.1)	0.918
Vomiting	1429	29 (2.0)	1449	33 (2.3)	0.701
Decreased activity	1447	271 (18.7)	1450	225 (15.5)	0.023
Decreased appetite	1439	104 (7.2)	1446	76 (5.3)	0.031

LAIV, live attenuated influenza vaccine and TIV, trivalent inactivated influenza vaccine.
[a] Number of subjects with known values.
[b] Fisher's exact test, 2-sided.
[c] Oral temperature.

rises of 0.7 and 1.3 from baseline, respectively. In the second study (N = 24), a more significant response was seen, with fold rises of 2.1 and 2.3, respectively. LAIV-induced cellular immune responses to influenza B, as measured by the ELISPOT assay, may be variable in older adults. It is worth noting that in the 2001 placebo-controlled study of LAIV in adults 60 years of age and older, no statistically significant efficacy against influenza B was observed [4]. It was hypothesized that the lack of observed efficacy could have been due to low circulation of influenza B, antigenic differences between the vaccine and circulating viruses, or lack of a protective immune response. However, in children, multiple studies have demonstrated that LAIV provides high efficacy against influenza B [11].

Interestingly, immunogenicity results by age group for TIV were consistent with previous descriptions of TIV efficacy by age group. HAI responses for all strains were lower in TIV recipients ≥70 years of age relative to recipients 60–69 years of age. This pattern is consistent with the results of the single randomized, placebo-controlled study of TIV in older adults, which reported lower vaccine efficacy among individuals ≥70 years of age relative to individuals 60–69 years of age [3].

Because of the critical importance of understanding vaccine-induced protection against influenza in older adults, post hoc analyses of serum HAI titers and ELISPOT counts in subjects with and without culture-confirmed influenza were conducted. These analyses revealed that a disproportionate number of culture-confirmed influenza illnesses occurred among baseline seronegative subjects; this was particularly true for those receiving TIV. This finding highlights the fact that older adults with low levels of pre-existing serum antibodies to targeted strains may represent the subgroup with the greatest risk for influenza illness, even after vaccination. Although previous influenza vaccination history was not collected in the study, influenza vaccination rates historically have been low in adults ≥60 years of age in South Africa despite recommendations for vaccination [17]. As a result, it is assumed that many subjects had not been previously vaccinated against influenza at enrollment.

Additionally, given that TIV is the current standard of care for influenza vaccination of older adults and postvaccination HAI response is considered a correlate of TIV-induced protection, it is notable who three-fourths of the TIV recipients that developed influenza did so despite achieving a seroprotective (i.e., ≥32) post-vaccination HAI titer. This finding suggests that further research into correlates of vaccine-induced protection in older adults may be warranted.

Acknowledgments

This study was sponsored by MedImmune and Wyeth. Wyeth was responsible for the design and conduct of the study, assisted in the collection, analysis, and interpretation of the data. All authors participated in the preparation, review, and approval of the manuscript. Medical writing and editorial assistance were provided by Susan E. DeRocco, PhD, and Gerard P. Johnson, PhD, of Complete Healthcare Communications, Inc. (Chadds Ford, PA, USA) and was funded by MedImmune.

References

[1] Nichol KL. Influenza vaccination in the elderly: impact on hospitalisation and mortality. Drugs Aging 2005;22:495–515.
[2] Data on file, MedImmune, Inc, Gaithersburg, MD.
[3] Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA 1994;272:1661–5.
[4] De Villiers PJ, Steele AD, Hiemstra LA, Rappaport R, Dunning AJ, Gruber WC, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. Vaccine 2009;28:228–34.
[5] The European Agency for the Evaluation of Medicinal Products. EMEA/CPMP Position statement on the use of placebo in clinical trials with regard to the revised declaration of Helsinki (EMEA/17424/01). <http://www.emea.europa.eu/pdfs/human/press/pos/1742401en.pdf>, 2011 (accessed 10.02.11).
[6] Forrest BD, Pride MW, Dunning AJ, Capeding MR, Chotpitayasunondh T, Tam JS, et al. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. Clin Vaccine Immunol 2008;15:1042–53.
[7] National Institute for Communicable Diseases. Recommendations pertaining to the use of viral vaccines: influenza. Review of influenza activity—2002. S Afr Med J 2003;93:271.
[8] Frank AL, Taber LH, Wells CR, Wells JM, Glezen WP, Paredes A. Patterns of shedding of myxoviruses and paramyxoviruses in children. J Infect Dis 1981;144:433–41.
[9] Ohmit SE, Victor JC, Teich ER, Truscon RK, Rotthoff JR, Newton DW, et al. Prevention of symptomatic seasonal influenza in 2005–2006 by inactivated and live attenuated vaccines. J Infect Dis 2008;198:312–7.
[10] Beran J, Wertzova V, Honegr K, Kaliskova E, Havlickova M, Havlik J, et al. Challenge of conducting a placebo-controlled randomized efficacy study for influenza vaccine in a season with low attack rate and a mismatched vaccine B strain: a concrete example. BMC Infect Dis 2009;9:2.
[11] Belshe RB, Coelingh K, Ambrose CS, Woo JC, Wu X. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine 2010;28:2149–56.
[12] Ambrose CS, Levin MJ, Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. Influenza Other Respir Viruses 2010;5:67–75.
[13] Treanor JJ, Kotloff K, Betts RF, Belshe R, Newman F, Iacuzio D, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine 1999;18:899–906.

[14] Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ 1993;307:988–90.
[15] Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. JAMA 1990;264:1139–41.
[16] Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis 2009;200:172–80.
[17] van Vuuren A, Rheeder P, Hak E. Effectiveness of influenza vaccination in the elderly in South Africa. Epidemiol Infect 2008:1–9.